

**METHODS AND COMPOSITIONS FOR TREATING OR PREVENTING
BACTERIAL INFECTION**

Technical Field

The invention relates to compositions and methods for treating or preventing diseases or disorders caused by or associated with certain bacterial infection, especially *Escherichia coli* (*E. coli*) or *Helicobacter pylori* (*H. pylori*) infection.

Background Art

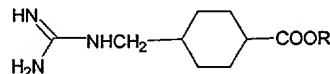
Ever since antibiotics became commercially available in the 1940s, they were regarded as magic bullets in eliminating bacteria without doing many harms to the patients. However, with each passing decade, an increasing number of antibiotics are no longer effective against a rising number of antibiotic resistant strains. Infections such as tuberculosis and pneumonia are becoming untreatable as they were before the discovery of antibiotics. We are now confronted with a serious worldwide public health crisis (Neu, *Science*, 257:1064-1073, (1992))

Since the discovery of penicillin in 1929, we now have over 150 antibiotics. They belong to several classes of antibiotics and have different mechanism of actions (Lyon and Skurray, *Microbiol. Rev.*, 51:88-134, (1987)). In general, these compounds are made by living organisms that inhibit growth and proliferation of bacteria. For example, vancomycin and β -lactam can block cell wall synthesis (Chopra et al., *Antimicrob. Agents Chemother.*, 41:497-503, (1997); and Nicolaou et al., *Scientific American*, 48-52 May (2001)). Erythromycin and tetracycline can disrupt protein synthesis. Sulfonamide interferes with folic acid metabolism, rifampin can block RNA synthesis, and quinolone inhibits DNA replication.

To combat the bacterial resistance, new approaches of treating bacteria infections are under research and development. These new approaches involve giving new life to existing antibiotics such as molecular alteration. Recently, a new class of antibiotics “self-assembling peptide nanotubes” generated interests (Associated Press New, July 25, 2001). This compound uses rings of microscopic amino acids that form tubes to push through the surface of bacterium. There are also many new developments in the genomic

areas. They entail interfering with bacterial RNA (rRNA) and messenger RNA (mRNA). A new technique called *in vivo* expression technology (IVET) that can tag bacteria genes is also under research. In addition, a promising approach is the antisense therapy for treating bacterial infections (Jasny et al., *Science*, 286:443-491, (1999)).

5 A class of antibacterial which seems to target a specific protease involved in DNA synthesis has been identified (Kato et al., *Biol. Pharm. Bull.*, 16:120-124 (1998); Irisawa et al., *Biol. Pharm. Bull.*, 16:621-626 (1993); Irisawa et al., *Biol. Pharm. Bull.*, 16:1211-1215 (1993); Kato et al., *J. Enzyme Inhibition*, 8:25-37 (1994); Kato et al., *Eur. J. Biochem.*, 210:1007-1014 (1992); and (Kato et al., *Biol. Pharm. Bull.*, 16:552-557 (1993)). This class of compounds, which acts as competitive trypsin inhibitors *in vitro*, is made up of various aromatic esters of trans-4-guanidinomethylcyclohexanecarboxylic acid (GMCHA) (See the following formula I):



10 *Helicobacter pylori* (*H. pylori*), a gram-negative spiral bacterium, was first isolated from a patient with chronic gastritis by Warren and Marshall in 1983 (Warren et al., *Lancet*, 1:1273-1275 (1983)). A lot of evidence has showed close relationship between gastroduodenal disease and *H. pylori*. Thus, it is assumed that *H. pylori* is an important bacterial pathogen which induces chronic gastritis and is associated with gastroduodenal ulcer, adenocarcinoma of the distal stomach, and gastric lymphoma in humans. Recently, the World Health Organization classified *H. pylori* as a group 1 carcinogen responsible for its leading role in the development of gastric cancer (International Agency for Research on Cancer. World Health Organization, Lyon, France, Monograph on the evaluation of carcinogenic risk to humans. 61:177-240, 1994).

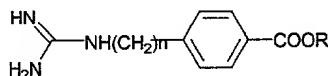
15 In 1994, National Institute of Health (NIH) recommended a regimen with simultaneous administration of proton-pump inhibitor (PPI) and antibacterial agent to eradicate *H. pylori* (*Helicobacter Pylori* in peptic ulcer disease: NIH consensus development panel on *Helicobacter Pylori* in peptic ulcer disease. (*JAMA*, 272:65-69 (1994)). Since then, oral administration of metronidazole, PPI, and clarithromycin and amoxicillin is put to practice, being able to cure the infection in up to 80-90% of the cases. However, the application of antibacterial agents causes a serious problem which induces the resistant strain of *H. pylori* to the reagent. Actually, the resistant strains to

methonidazole, clarithromycin and amoxicillin have already been reported (Zwet et al., *Lancet*, 352:1595 (1998)). Other severe problems caused by the administration of PPI and antibacterial agent are that PPI induces indigestion and large amounts of antibacterial agent result severe in destruction of the bacterial flora in digestive tract.

5 Therefore, it is very important to find out a new type of active anti-bacteria compound. The present invention addresses this and other related needs in the art.

Disclosure of the Invention

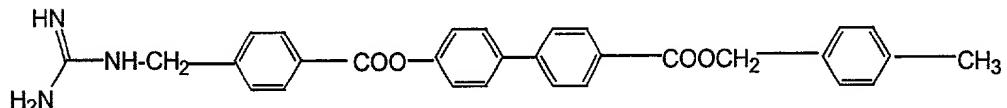
10 The present invention adds to the repertoire of anti-bacteria agents by providing drugs which would inhibit DNA replication initiation in certain bacteria. In one aspect, the present invention is directed to a compound, or a pharmaceutically acceptable salt thereof, having the following formula II:



15 wherein n is an integer from 0-1, and R is elected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ aryl and



Preferably, the compound has the following formula III (NE-2001):



20 Also preferably, the compound, or its pharmaceutically acceptable salt thereof, is provided in the form of a pharmaceutical composition, either alone or in combination with a pharmaceutically acceptable carrier or excipient. Kits comprising the above compounds for treating or preventing a disease or disorder caused by or associated with bacterial infection, e.g., *E. coli* or *H. pylori* infection, are also provided.

25 In another aspect, the present invention is directed to a method for treating or preventing a disease or disorder caused by or associated with bacterial infection, which